Influenza Update

A Review of Currently Available Vaccines

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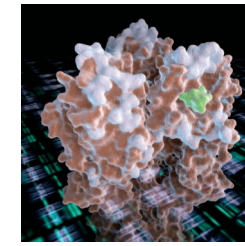

INTRODUCTION

Influenza is a highly contagious respiratory illness that is responsible for significant morbidity and mortality. Approximately 9% of the world's population is affected annually, with up to 1 billion infections, 3 to 5 million severe cases, and 300,000 to 500,000 deaths each year.[1–3]

In the U.S. alone, nearly 20% of the population is affected. On average, 25 to 50 million documented influenza cases, 225,000 hospitalizations, and ultimately more than 20,000 deaths occur every year.[1,2,4–7]

Major changes in the surface antigens hemagglutinin (HA) and neuraminidase (NA) occur sporadically (in 10- to 40-year increments), leading to pandemic disease with increased morbidity and mortality rates.[8] The most recent major change or antigenic shift occurred during the 2008–2009 influenza season, with the introduction of novel influenza A (H1N1).[9,10]

Although influenza can affect individuals of all ages, most influenza-related deaths occur in the elderly (65 years of age and older) and in those with underlying cardiovascular and respiratory comorbidities.[8,11–13] The elderly make up almost 15% of the U.S. population but represent 65% of the hospitalizations and 90% of the deaths associated with influenza.[14] In 2006, influenza and pneumonia were the eighth leading cause of deaths, overall, in the U.S. and the seventh leading cause of death in the elderly.[15]

Influenza is also associated with a substantial economic burden. In 2003, 24.7 million influenza cases occurred in the U.S., with 31.4 million flu-related outpatient office visits, 334,185 hospital stays, and 41,008 deaths. This resulted in 44 million lost days of productivity and 610,656 life-years lost secondary to the flu. The estimated economic burden of influenza totaled $87.1 billion, with $10.4 billion spent in direct medical costs. Most of the total costs (64%) were attributed to patients 65 years of age and older, whereas 21%, 10%, and 5% of costs were expended on patients 50 to 64 years of age, patients 18 to 49 years of age, and children, respectively. Of the $10.4 billion in total medical costs, 40% ($4.2 billion) was spent on treatment of the elderly.[16]

Vaccination is seen as the best option to prevent, control, and decrease the socioeconomic burden of influenza.[1,4,8,13,17,18] Nine influenza vaccines are currently on the market (Table 1).[9,19] Each vaccine contains the same three viral influenza strains that the Centers for Disease Control and Prevention (CDC) determines to be the most predominant circulating strains for that flu season. Typically, this includes two type A strains (H3N2, H1N1) and one type B strain.

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Accepted for publication on August 25, 2011.

THE INFLUENZA VIRUS

Antigenic Changes

To maintain its virulence within a population, the influenza virus continuously evolves. Two types of antigenic changes can occur. Antigenic *drift* results from the accumulation of point mutations in the *HA* and *NA* genes. When drift occurs, seasonal epidemics can arise; this is why the influenza vaccine is updated on an annual basis. Antigenic *shift* is the appearance in the human population of a new influenza virus that contains novel HA or NA proteins, or both, that are immunologically distinct from those circulating in recent years. Unlike drift, which occurs yearly, shift is an unpredictable event.[8–10,17, 20,21]

The 2009 H1N1 Pandemic

Beginning on April 15, 2009, the world witnessed its first influenza pandemic in nearly 40 years. H1N1 was a quadruple-reassortant virus that contained genes from four different sources. The influenza virus consists of eight gene segments: *HA, NA*, matrix gene, nucleoprotein (NP), nonstructural gene (*NS*), polymerase acidic *(PA)*, polymerase basic 1 *(PB1)*, and polymerase basic 2 *(PB2)*.

In the novel influenza A (H1N1) virus, three gene segments *(PB1, PB2*, and *PA)* came from North American swine triple-reassortant viruses. Both the *PB2* and *PA* genes were originally avian viruses that entered North American swine, whereas *PB1* originated in birds, was transferred to humans, and then made its way to North American swine. Another three genes *(HA, NP*, and *NS)* were classical swine viruses that evolved

Table 1 Influenza Vaccines Recommended For 2011–2012

Trade Name	Manufacturer
Afluria	CSL Biotherapies
Agriflu	Novartis Vaccine and Diagnostics
Fluarix	GlaxoSmithKline Biologicals
FluLaval	ID Biomedical Corp. of Quebec (subsidiary of GlaxoSmithKline)
FluMist	MedImmune
Fluvirin	Novartis Vaccine and Diagnostics
Fluzone	Sanofi Pasteur
Fluzone High-Dose	Sanofi Pasteur
Fluzone Intradermal	Sanofi Pasteur

Data from Fiore AE, et al. *MMWR Recommendations Rep* 2010;59(RR 08):1–62[9] and the Centers for Disease Control and Prevention.[19]

Disclosure: Dr. Clayville reports that she has no financial or commercial relationships in regard to this article.

from avian sources. Finally, the *NA* and matrix gene segments originated as an avian virus and subsequently entered the Eurasian swine population.[22–24]

According to CDC estimates, between 43 million and 89 million cases of novel influenza A (H1N1) occurred from April 2009 to April 2010. Between 195,000 and 403,000 individuals were hospitalized, and between 8,870 and 18,300 people died. Of those patients who died, 90% had underlying medical conditions. In children and adolescents ranging from 5 to 17 years of age, hospitalization rates were two to five times higher than those usually seen with seasonal influenza.[25]

Several key differences between the 2009 H1N1 influenza virus and the seasonal influenza virus were identified. In addition to the classic influenza symptoms of fever, myalgias, nonproductive cough, and headache, approximately 25% of individuals infected with the H1N1 virus experienced gastrointestinal (GI) symptoms of vomiting and diarrhea.[24,26]

Typically, the rate of seasonal influenza is highest in the elderly. This was not the case, however, with the 2009 H1N1 influenza pandemic; the highest incidence was among young, school-aged children. One explanation for this difference is the fact that 5- to 24-year-olds are typically in school, where the virus can easily spread. Another theory is that individuals older than 65 years of age grew up in the 1950s, when the dominant influenza strains were H1N1 in nature, and this might have conferred some protection against the 2009 H1N1 strain.[26] Finally, seasonal influenza typically peaks in either January or February. During the 2009 H1N1 pandemic, the U.S. experienced major flu activity in the spring and fall, especially during the second week of October, which is in contrast to what is typically seen with seasonal influenza.[26]

For the 2009–2010 influenza season, the CDC recommended that individuals receive both the 2009–2010 seasonal influenza vaccine and the 2009 H1N1 monovalent vaccine. Anticipating that the 2009 H1N1 influenza A strain would be the predominant H1N1 strain in circulation the following year, and aiming to decrease the number of injections that patients would have to receive, the CDC recommended that clinicians use the A/California/7/2009 (H1N1)-like strain from the monovalent vaccine as one of the three components in the 2010–2011 trivalent seasonal influenza vaccine.

VACCINE EFFICACY

Ensuring that an influenza vaccine works is of the utmost importance. A vaccine's effectiveness is determined by its ability to prevent illness and depends on various factors, such as (1) the way in which the vaccine is handled and administered; (2) the antigenic match between the vaccine and the circulating virus; and (3) the recipient's age, health status, use of medications that affect immune function, influenza vaccination history, and pre-vaccination antibody titer levels.[4,27,28]

A vaccine's immunogenicity is directly correlated to the recipient's HA immunoglobulin G (IgG) levels after vaccination.[4] These anti-HA antibodies, assessed by the HA inhibition test, specifically inhibit the attachment of the influenza virus to its receptor on respiratory cells. The concentration of these antibodies determines whether the vaccine recipient will be protected from infection or will experience decreased disease severity.[29]

To achieve 50% protection against infection, HA antibody titers of 30 to 40 are needed.[30] Higher titers (120 to 160) provide greater protection.[31–33] In general, HA antibody titers of 1:40 or greater provide antiviral protection.[29] The rate of protection varies, depending on the antigenic match between the vaccine and the circulating virus.[34–39] When the vaccine closely matches the circulating viral strains, efficacy rates in individuals younger than 65 years of age typically range from 80% to 90%.[33] A close match protects only about 30% to 40% of elderly adults.[9,40]

RECOMMENDATIONS

The optimal approach to preventing influenza illness, its potential complications, and its spread to others is through immunization. In February 2010, the Advisory Committee on Immunization Practices (ACIP) expanded its influenza recommendation to encourage all individuals 6 months of age and older, without contraindications, to receive the yearly influenza vaccine.[9]

The ACIP recommends several types of influenza vaccines (Table 2).[9] Each vaccine should be stored and shipped refrigerated at 35 F to 46°F (2° to 8°C).[9,41] Although all available influenza vaccines contain the same three antigenically equivalent viral strains, there are differences in their makeup.

In a trivalent influenza vaccine (TIV), the virus has been killed or "inactivated" chemically in the manufacturing process and therefore cannot cause infection. These vaccines are given via intramuscular (IM) injection (in individuals 6 months of age and older) in the deltoid muscle in adults and older children and in the anterolateral aspects of the thigh in infants and young children. Standard-dose TIVs contain 15 mcg of each HA strain, for a total of 45 mcg. Infants and toddlers 6 to 36 months of age may receive a vaccine containing half that dose. In October 2010, the FDA approved a high-dose TIV containing 60 mcg of each influenza strain for adults 65 years of age and older. More recently, the FDA approved an intradermal TIV that delivers 9 mcg per influenza strain in a 0.1-mL prefilled microinjection system.[9,41]

One live attenuated influenza vaccine (LAIV) is currently on the market (FluMist, MedImmune). This vaccine is administered intranasally and contains a live virus; therefore, it has the potential to cause mild symptoms (rhinorrhea, nasal congestion, fever, and sore throat) similar to those that occur during influenza illness. It is given as a 0.2-mL (divided) nasal spray to healthy, nonpregnant individuals 2 to 49 years of age. Because of a lack of safety data, LAIV is not recommended for persons with underlying medical conditions, those 2 to 4 years of age with asthma or wheezing within the past year, and family members or close contacts with severe immunosuppression.[9,41]

The FDA recommends that the 2011–2012 seasonal influenza vaccine contain the following three influenza strains: A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like. These are the same viral strains that were used in the 2010–2011 seasonal influenza vaccine.[19]

NEW INFLUENZA VACCINE OPTIONS

High-Dose Influenza Vaccine

Because a person's level of protection against influenza is correlated with the concentration of anti-HA antibodies, it was proposed that increasing the amount of antigen within an

Currently Available Influenza Vaccines

Table 2 Influenza Vaccines Recommended by the Advisory Committee on Immunization Practices (ACIP)

Vaccine Type	Trade Name	Dosage Form	Mercury Content (mcg Hg/dose)	Age Group
TIV	Afluria	0.5-mL prefilled syringe	0	≥ 9 years
	Agriflu	0.5-mL prefilled syringe	0	≥ 18 years
	Fluarix	0.5-mL prefilled syringe	0	≥ 3 years
	FluLaval	5-mL multidose vial	25	≥ 18 years
	Fluvirin	5-mL multidose vial	25	≥ 4 years
		0.5-mL prefilled syringe	< 1	
	Fluzone	0.25-mL prefilled syringe	0	6–35 months
		0.5-mL prefilled syringe	0	≥ 3 years
		0.5-mL vial	0	
		5-mL multidose vial	25	≥ 6 months
TIV high-dose	Fluzone High-Dose	0.5-mL prefilled syringe	0	≥ 65 years
TIV intradermal	Fluzone Intradermal	0.1-mL prefilled microinjection system	0	18–64 years
LAIV	FluMist	0.2-mL sprayer, divided dose	0	2–49 years

LAIV = live attenuated influenza vaccine; TIV = trivalent influenza vaccine.
Data from Fiore AE, et al. *MMWR Recommendations Rep* 2010;59(RR 08):1–62.[9]

influenza vaccine might be able to overcome the decreased response seen in older people. To determine the safety and effectiveness of increased antigen in older individuals, Keitel et al. randomly assigned 202 persons 65 years of age and older (mean age, 72.4 years) to receive a single IM injection of placebo or TIV containing 15, 30, or 60 mcg of the HA antigen per strain. Blood samples were collected before and 1 month after immunization, and participants were examined for adverse events (AEs) at 30 minutes and at 2 and 28 days after injection.[42]

In terms of effectiveness, statistically significant ($P < 0.001$) increases in geometric mean titer (GMT) values were observed for the three amounts of antigen tested, regardless of whether participants had higher or lower pre-vaccination antibody titers. Significant dose-related increases in antibody responses were seen for both type-A strains but not for the type-B strain, especially in subjects with lower pre-vaccination titers. In these individuals, antibody titers were nearly doubled after injection of the vaccine containing 60 mcg of HA antigen per strain, compared with the 15-mcg vaccine.[42]

Rates of seroconversion in subjects with pre-vaccination titers of 8 or less were 60%, 82%, and 100% to the H1N1 strain and 50%, 63%, and 80% to the H3N2 strain for the 15-, 30-, and 60-mcg vaccines, respectively. Controlling for age, sex, body mass index (BMI), previous immunizations, previous influenza-like illness, and pre-vaccination titers also showed significant dose-related effects.[42]

All doses were considered safe and well tolerated, but significant dose-related increases in injection-site discomfort ($P < 0.001$) and redness or swelling ($P = 0.005$) were observed, especially in the 60-mcg group compared with the 15-mcg group ($P = 0.04$). Similar rates of systemic symptoms were seen in all groups 1 week after vaccination.[42]

Based on positive safety and efficacy results in previous studies, two clinical trials were conducted to compare a high-dose TIV (60 mcg per strain) with a standard-dose TIV (15 mcg per strain).[43,44]

In a phase 2, multicenter, randomized, double-blind, stratified study, 414 subjects 65 years of age and older were assigned to receive either a 180-mcg vaccine (60 mcg per strain) or a 45-mcg vaccine (15 mcg per strain) to determine (1) the number of patients with seroconversion, (2) the GMTs for each group, and (3) the proportion of those with HA titers of 1:32 or greater, 1:64 or greater, and 1:128 or greater. Safety endpoints of local and systemic reactions were also evaluated.[43]

Twenty-eight days after vaccination, serum antibody levels increased significantly ($P < 0.001$) with both the high-dose and standard-dose vaccines when compared with baseline values. The overall rate of seroconversion was significantly greater in the high-dose group than in the standard-dose group (27.9% vs. 16.8%, respectively; $P < 0.01$).[43]

In previously vaccinated subjects, significantly increased seroconversion rates were seen for all three antigens (H1N1, 24.2%; H3N2, 14.2%; type B, 17.8%; $P \leq 0.01$). In persons who were not previously vaccinated, increased seroconversion rates were observed for the H1N1 (39.6%; $P < 0.01$) and H3N2 (24.7%; $P < 0.02$) antigens but not for the type B antigen (18.1%; $P = 0.1$).[43]

Before vaccination, GMT values for the two type A strains were similar in both vaccine groups, but GMT values were higher for the type B strain in the standard-dose group. After immunization, GMT values significantly increased across the board ($P < 0.0001$). The high-dose group had statistically

greater GMT increases ($P \leq 0.01$) compared with the standard-dose group in all categories except for the type B strain in previously unvaccinated subjects.[43] More subjects in the high-dose group had HA titers of 1:32 or greater, 1:64 or greater, or 1:128 or greater compared with the standard-dose group.[43]

In the high-dose group, significantly more subjects ($P < 0.05$) responded to the H1N1 antigen compared with the standard-dose group regardless of previous vaccination status. Although higher response rates to the H3N2 antigen were seen in the high-dose population (89% to 100% had titers of 1:32 or greater), significantly increased rates ($P < 0.05$) were observed only in subjects without a previous vaccination and at the 1:64 cutoff in the total group.[43]

For the type B antigen, significantly increased seroconversion rates ($P < 0.05$) were observed in pre-vaccinated subjects and at the 1:64 cutoff in the total group.[43]

In general, subjects in the high-dose group reported more AEs than did those in the standard-dose group at 1 week after vaccination. Moderate or severe local and systemic reactions were more common in the high-dose group than in the standard-dose group, but only localized pain and systemic myalgias occurred more often with the high-dose vaccine ($P < 0.01$). At 7 months after vaccination, a total of 22 subjects (5.3%) reported a serious AE, although none was considered to be related to vaccination.[43]

In a phase 3, multicenter, randomized, double-blind study, 3,876 individuals 65 years of age and older were randomly assigned, in a 2:1 ratio, to receive a high-dose or standard-dose TIV.[44] Those in the high-dose group were further randomly assigned to receive one of three different vaccine lots. Blood samples were collected before and 28 days after vaccination to assess immunogenicity in terms of both lot consistency and superiority of the high-dose vaccine. Superiority was determined by the ratio of GMTs (high dose/standard dose above 1.5) and by the four-fold difference in increased HA antibody titers (high dose/standard dose above 10%).

To be considered superior to the standard-dose vaccine, the high-dose vaccine had to demonstrate superiority for at least two of the vaccine strains without being inferior to any of the strains. Safety endpoints were also analyzed.[44]

On day 28, an analysis of blood samples showed positive GMT ratios—H1N1 (1.7, 1.6–1.8), H3N2 (1.8, 1.7–2), and B (1.3, 1.2–1.4)—as well as significantly higher rates of seroconversion—25.4% (H1N1), 18.4% (H3N2), and 11.8% (B)—for the high-dose vaccine. According to the defined criteria, the high-dose vaccine was found to be superior to the standard-dose vaccine for the two type A strains and non-inferior to the type B strain, thus meeting the stated overall superiority criteria (Table 3). Further analyses showed some differences in patients based on sex, advanced age, and pre-vaccination titers. Both men and women had a greater response to the high-dose vaccine than to the standard vaccine, but the women had a greater response to both vaccines.[44]

Although having a history of cardiopulmonary disease in the very elderly did not show a statistically significant difference in GMT values compared with younger elderly patients, the overall improved effect of the high-dose vaccine was maintained in the very elderly with cardiopulmonary disease. In addition, patients with low pre-vaccination titers (below 1:10) also showed greater GMT values when they were given the high-dose vaccine instead of the standard vaccine (H1N1, 83 vs. 45; H3N2, 283 vs. 124; and B, 42 vs. 27; $P < 0.001$).[44]

Both local and systemic reactions were more common in the 7 days following vaccination with the high-dose vaccine compared with the standard vaccine (Figure 1). Common local reactions included pain (36% with the high dose vs. 24% with the standard dose), erythema (15% with the high dose vs. 11% with the standard dose), and swelling. Most systemic reactions seen with the high-dose vaccine were mild; typically resolved within 3 days; and were non-inferior with respect to headache, malaise, myalgia, and fever, and inferior to the standard vaccine with respect to moderate or severe fever, for a relative risk (RR) of 3.6 (1.25–10.08).[44]

The FDA has approved Fluzone High-Dose vaccine (Sanofi Pasteur) for the prevention of influenza in persons 65 years of age and older; however, the ACIP has issued a only provisional recommendation for the use of this vaccine until post-marketing studies have been completed.

Intradermal Influenza Vaccine

A major barrier to influenza immunization is a fear of needles and injections. To overcome this fear, Becton Dickinson

Table 3 A Comparison of High-Dose and Standard-Dose Vaccines in Elderly Patients

	GMT			Seroconversion			Seroprotection		
	Vaccine	*No.*	*GMT Ratio (95% CI)*	*Vaccine*	*No.*	*Percent Difference (95% CI)*	*Vaccine*	*No.*	*Percent Difference (95% CI)*
H1N1	HD SD	2,543 1,252	1.7* (1.6–1.8)	HD SD	2,531 1,249	25.4* (22.4–28.5)	HD SD	2,543 1,252	13.1* (10.5–15.8)
H3N2	HD SD	2,544 1,252	1.8* (1.7–2)	HD SD	2,531 1,248	18.4* (15.1–21.7)	HD SD	2,544 1,252	2.8 (1.7–3.9)
B	HD SD	2,542 1,252	1.3 (1.2–1.4)	HD SD	2,529 1,249	11.8 (8.6–15)	HD SD	2,542 1,252	11.7 (8.7–14.7)

*The high-dose (HD) vaccine was superior to the standard-dose (SD) vaccine.
CI = confidence interval; GMT = geometric mean titer.
Data from Falsey AR, et al. *J Infect Dis* 2009;200:172–180.[44]

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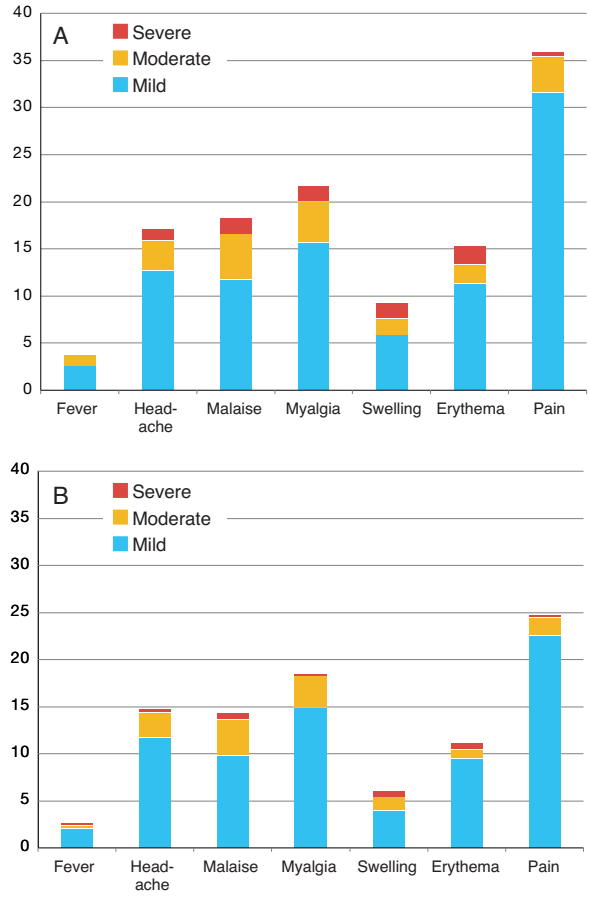

Figure 1 Local and systemic adverse events with high-dose (A) and standard-dose (B) influenza vaccines. (From Falsey AR, et al. *J Infect Dis 2009*;200:172–180. By permission of Oxford Journals.[44])

(BD) developed a microinjection system that delivers a consistent volume to the dermal layer via a 30-gauge, 1.5-mm long needle. Intradermal administration delivers the antigen directly to dendritic cells in the skin to initiate an immune response. In addition, some of the injected vaccine may diffuse backward across the basement membrane to be captured by epidermal Langerhans cells.[45,46]

In a study conducted to determine its immunogenicity, 978 patients 18 to 57 years of age were randomly assigned, in a 2:1 ratio, to receive either the intradermal vaccine (9 mcg per HA strain) or the standard IM vaccine.[45] The intradermal vaccine was noted to be superior to the standard vaccine with respect to the two type A strains and non-inferior to the type B strain, with seroprotection rates greater than 90% for each.

High seroprotection rates continued to be observed 3, 6, and 12 months after the vaccination. Patients receiving the intradermal vaccine experienced increased rates of injection-site reactions exceeding 5 cm in diameter for more than 3 days (0.2% vs. 0%) and fever for 24 hours or more (1.5% vs. 0.8%) compared with the standard vaccine.[45]

In a large-scale study of 2,225 patients 18 to 60 years of age, three lots of an intradermal vaccine were compared with the standard vaccine.[46] The intradermal vaccine delivered 0.1 mL containing 9 mcg of each influenza strain via BD's microinjection system, and the standard vaccine delivered 0.5 mL containing 15 mcg of the same influenza strains via IM injection.

Table 4 Seroprotection Rates of Intradermal and Intramuscular Influenza Vaccines

Route	H1N1	H3N2	B
Intradermal	87.2% (85.2–89)	93.5% (92–94.8)	72.9% (70.4–75.3)
Intramuscular	86.2% (82.6–89.3)	95.4% (93–97.2)	74.8% (70.4–78.8)

Data from Arnou R, et al. *Hum Vaccines* 2010;6:346–354.[46]

Twenty-one days following vaccination, the intradermal vaccine was non-inferior to the IM vaccine (Table 4). More patients experienced visible injection-site reactions that were characterized by erythema, swelling, induration, and mild pruritus with the intradermal vaccine, compared with the IM vaccine (Table 5). This reaction was expected, because the immunological and inflammatory reactions occurred closer to the skin's surface with the intradermal vaccine. These reactions were temporary and not associated with increased pain.[46]

Fluzone Intradermal (Sanofi Pasteur) was approved in May 2011 for the prevention of influenza in patients 18 to 64 years of age. The vaccine is available in a single-dose, preservative-free, prefilled microinjection system syringe. Current studies are also under way to evaluate a high-dose intradermal vaccine for patients 65 years of age and older.

FUTURE VACCINES UNDER INVESTIGATION

Intradermal Vaccine for the Elderly

Two studies are examining the effects of an intradermal influenza vaccine in older adults. In a trial of 258 individuals (mean age, 74.8 years), Chi and associates randomly assigned

Table 5 Adverse Reactions With Intradermal and Intramuscular Influenza Vaccines

Reaction	Intradermal	Intramuscular
Injection-site		
• Erythema	84.4% (82.6–86)	25.5% (21.5–29.8)
• Swelling	61.9% (59.6–64.1)	20.7% (17.0–24.8)
• Induration	60.8% (58.5–63.1)	26.1% (22.1–30.5)
• Pain	43.1% (40.8–45.5)	48.4% (43.7–53.2)
• Pruritus	44.8% (42.5–47.2)	13.1% (10.1–16.6)
• Ecchymosis	10.0% (8.6–11.5)	9.9% (7.3–13.1)
Systemic		
• Headache	29.2% (27.1–31.3)	30% (25.7–34.5)
• Myalgia	23.5% (21.6–25.6)	29.5% (25.3–34)
• Malaise	18.2% (16.9–20.1)	19.4% (15.8–23.4)
• Shivering	9.4% (8.1–10.9)	7.4% (5.2–10.3)
• Fever	3.9% (3.0–4.9)	3.4% (1.9–5.5)

Data from Arnou R, et al. *Hum Vaccines* 2010;6:346–354.[46]

participants to receive a standard 15-mcg 0.5-mL IM vaccine; a 9-mcg 0.3-mL IM vaccine; a 9-mcg 0.3-mL intradermal vaccine; or two doses of a 9-mcg 0.15-mL intradermal vaccine.[47] Similar seroprotection rates were seen for all groups:

- H1N1: 65.6%, 57.8%, 68.9%, and 67.2%
- H3N2: 76.6%, 75%, 75.4%, and 75%
- B: 26.6%, 17.2%, 16.4%, and 25%

Local injection-site reactions of redness, swelling, and itching were significantly higher with intradermal injections.[47]

In another trial involving 1,101 patients, Holland et al. compared a 15-mcg per strain vaccine and a 21-mcg per strain intradermal vaccine with a standard 15-mcg IM vaccine.[48] The superiority of the intradermal vaccines was observed if the lower limit of the 95% confidence interval (CI) exceeded 1. GMTs were increased in all groups but were higher in the two intradermal groups. Both intradermal vaccines were superior ($P < 0.0001$) to the standard vaccine. GMTs were 48% to 70% higher than that seen with the standard vaccine. No statistical significance was observed between the 21-mcg and 15-mcg intradermal vaccines. Malaise and injection-site ecchymoses were similar in all three groups, but other injection-site reactions were more common in the two intradermal vaccine groups.[48]

Avian H5N1 Vaccine

Even though influenza A (H1N1) has received the most attention lately, avian-origin influenza A (H5N1) strains have been reported annually and continue to remain a threat, especially since the re-emergence of avian flu in 2003. Before then, human cases resulted only from close contact with infected poultry. Unfortunately, avian flu carries a high mortality rate (above 60%) and maintains the ability to experience antigenic drift, which can cause human-to-human transmission.[49–51]

Currently, the AS03-adjuvanted H5N1 A/Vietnam/1194/04 (NIBRG-14) vaccine (Prepandrix, GlaxoSmithKline) is approved in Europe for adults 18 years of age and older as a "prepandemic" vaccine to be produced and stockpiled in the event that an outbreak occurs. Another $AS03_A$-adjuvanted A/Indonesia/05/2005 vaccine has recently undergone phase 3 clinical trials to be tested in adults 18 to 64 years of age and in the elderly.[51]

Participants (n = 4,561) were randomly assigned, in a 3:1 ratio, to receive the vaccine or placebo. Those in the vaccine group were further randomly assigned, in a 1:1:1 fashion, to compare vaccine lot consistency. Each vaccine contained 3.75 mcg of H5N1 HA. Participants received the first dose on day 0 in the nondominant arm and a second dose 21 days later in the dominant arm. On day 42, anti-HA antibody levels were assessed. In the 18- to 64-year-olds, seroprotection rates equaled 90.8% (CI, 89.3–92.2%) and 74.5% (CI, 69.9–78.7%) in the elderly group compared with the placebo group, which experienced protection rates of 0% to 8.3%. Pain was considered to be the most common local adverse reaction in the vaccinated patients and lasted for an average of 2.8 days.[51]

SPECIAL POPULATIONS

Even though it is now recommended that all individuals 6 months of age and older be vaccinated, certain populations need special attention in the event of vaccine shortages.

Children

Although children do not typically have the highest mortality rates from influenza, they do have the highest influenza attack rates during community outbreaks, and they can easily transmit the virus to others. It has been proposed that by vaccinating children against the flu, the number of cases within the community will decrease indirectly via herd immunity.[9,52]

Current recommendations state that all children 6 months of age and older should be vaccinated. Children 6 months to 8 years of age who are receiving the vaccine for the first time should receive two doses, separated by four weeks. If the child received only one dose the previous season and that was the first influenza vaccination, the child should also receive two doses, separated by 4 weeks.[9,52]

The need for two influenza doses comes from immunogenicity studies conducted with the 2009 H1N1 monovalent vaccine showing that children 9 years of age and younger had lower antibody levels and lower protection rates with a single vaccine dose compared with children receiving two doses. In a study of 370 healthy infants and children between 6 months and 9 years of age, seroprotection rates were 92.5% (95% CI, 87.6–95.6%) following a single vaccine dose and 100% 21 days later following a second dose.[53]

The following TIV vaccines are available for children: Fluzone (Sanofi Pasteur), Fluvirin (Novartis), Fluarix (GlaxoSmithKline), and Afluria (CSL Biotherapies). Children older than 2 years of age can also receive LAIV if they do not have any underlying medical conditions and have not had a wheezing episode within the previous year.[9,52]

Older Patients

One of the hallmarks of aging is immunosenescence or a decrease in immune function, namely cell-mediated immunity.[54] As people age, the decline in thymic tissue leads to a reduction in the naive T-cell population. The total number of T cells does not change, but the cells change and proliferate; this can lead to an increased risk of replication error and the production of more T cells that are less able to mount an appropriate immune response.[55,56] These less active T cells may be responsible for the poor protection and the prolonged and severe infection seen in the elderly.[14] Therefore, adequate HA titers following vaccination might not provide adequate immunity in this population, and a statistical increase in titers that correlate with protection might not correlate with clinical improvements in the elderly.[54]

Patient-related and drug-related variables can affect how older people respond to influenza vaccinations. In a 1989 review conducted by Beyer et al., having a serious illness, using immunosuppressant medications, receiving a previous influenza vaccine, and having high pre-vaccination antibody titers can influence a vaccine's effectiveness in older patients.[57] A patient's living situation and medical history, as well as the vaccine's antigen dose and route of administration, may also affect response.[40]

As for age alone, seroconversion and seroprotection rates for all three antigens tested (H1N1, H3N2, and B) were significantly higher in the younger population (17–59 years of age) than in the older group (58–104 years) ($P < 0.001$).[40] Adjusting for age, the investigators found that younger patients had a three-fold to four-fold better response to the H1N1 and B antigens and a

two-fold better response to the H3N2 antigen compared with the older patients. When comparing both adjusted and unadjusted antibody responses in the elderly group younger than 75 years of age with the very elderly patients (75 years of age and older), the very elderly had significantly lower seroprotection values to the H1N1 and H3N2 antigens ($P < 0.001$) and higher seroprotection values to the B antigen ($P < 0.001$).[40]

Previous vaccination, high pre-vaccination antibody titers, and residence were also variables that produced differences in response to influenza vaccination. In the young-versus-elderly analysis, previous influenza vaccination produced significantly lower seroprotection rates to the H3N2 (odds ratio [OR], 0.76) and B (OR, 0.24) antigens, whereas high pre-vaccination antibody titers had higher seroprotection rates (range, 2.25–8.74). Living in a nursing home or a long-term care facility provided higher seroprotection rates (range, 1.56–3.69) for all three antigens.

Interestingly, seroprotection rates for institutionalized elderly patients (80%) were similar to those seen in young non-institutionalized patients (84%) with respect to the H3N2 antigen. In the younger elderly and very elderly groups, high pre-vaccination antibody titers produced higher seroprotection rates. Previous influenza vaccination was associated with decreased seroprotection rates, but the effect was less substantial. Institutionalized elderly patients also responded more favorably to vaccination than their non-institutionalized counterparts (range, 1.55–3.44).[40]

In the high-risk elderly population, influenza vaccination has been shown to decrease the rate of complications and mortality.[57–59]

In a study of 147,551 older individuals, Nichol et al. found an overall decrease in the rate of hospitalizations for pneumonia and influenza (39%; $P < 0.001$), all respiratory conditions (32%; $P < 0.001$), and congestive heart failure (27%; $P < 0.001$), as well as a 50% decrease in all-cause mortality ($P < 0.001$).[59] High-risk individuals were defined as having heart or lung disease. Intermediate-risk individuals had diabetes, renal disease, rheumatological disease, or dementia, or stroke without underlying heart or lung disease. Low-risk persons had none of these conditions. In a comparison of vaccinated and non-vaccinated persons in the high-risk population, the number of hospitalizations declined for pneumonia and influenza (29%; $P = 0.002$), acute or chronic respiratory conditions (19%; $P = 0.001$), and all-cause death (49%; $P < 0.001$) but not for congestive heart failure (14%; $P = 0.07$). These results are similar to those in the low-risk group; however, in the intermediate-risk group, there was a statistically significant decline in all-cause mortality (64%; $P < 0.001$) but not in any other metrics.[59]

Wang and colleagues found a significant benefit in mortality not only in influenza-related pneumonia and chronic obstructive pulmonary disease (COPD) during the influenza season but also in mortality for other long-term complications during or after the influenza season after making adjustments for age, sex, and risk status.[60] In this study, high-risk persons were defined as having (1) a history of hospital admissions three years before the study; (2) a chronic condition, such as tuberculosis, cirrhosis, or other cardiovascular, pulmonary, metabolic, renal, or neurological disorder; (3) a severe case of disease, such as a solid-organ cancer, hemoglobinopathies, severe injury, burn injury, HIV infection, systemic autoimmune syndromes with immunosuppressive therapy, a solid-organ transplant, or chronic psychosis. Residence in a nursing home or other long-term-care facility was also a risk factor.

In both the high-risk group (n = 21,347) and the low-risk group (n = 81,351), there was a significant relative risk reduction (RR) ($P < 0.05$) as follows:

- All-cause mortality: 0.44 (0.25–0.72) and 0.59 (0.63–0.66)
- Mortality rates associated with:
  - Stroke: 0.25 (0.21–0.36) and 0.45 (0.3–0.65)
  - Pneumonia: 0.35 (0.23–0.54) and 0.51 (0.31–0.83)
  - COPD: 0.45 (0.32–0.63) and 0.47 (0.26–0.83)
  - Diabetes: 0.41 (0.31–0.54) and 0.58 (0.33–0.99)
  - Renal disease: 0.4 (0.22–0.68) and 0.32 (0.15–0.71)

High-risk elderly individuals also experienced significant declines in heart disease, chronic liver disease, and neoplasms.[60]

Patients With High-Risk Medical Conditions

Patients with certain underlying medical conditions are at an increased risk for influenza-related complications. Patients considered to be at high risk have chronic pulmonary conditions, including asthma; cardiovascular disease, excluding isolated hypertension; renal and hepatic disease; neurological conditions, including cognitive dysfunction, spinal cord injuries, seizure disorders, and neuromuscular disorders; hematological disorders; and metabolic disorders, including diabetes. Recent additions to this list include morbidly obese persons, American Indians, and Alaska Natives; these groups have a high prevalence of underlying chronic conditions that may be unknown to the patient or the health care provider.[52]

Individuals who live with or work in close contact with severely immunosuppressed persons, including health care professionals, should be vaccinated with TIV to reduce the risk of influenza transmission. Even if immunocompromised individuals are vaccinated, they may be inadequately protected against the flu. LAIV is not recommended because there is a theoretical risk that the virus could be transmitted to them, although this has not been documented. It is currently recommended that if health care professionals have received LAIV, they should avoid contact with immunocompromised individuals for seven days.[52]

Pregnant Women

Influenza vaccination is recommended for all pregnant and breast-feeding women because infants and children younger than 5 years of age are at an increased risk for influenza complications and hospitalization if they become infected. Pregnant women should be given a preservative-free TIV. The manufacturers of Fluzone, Fluarix, and Afluria have preservative-free vaccines that can be used. Unless there are contraindications, postpartum and breast-feeding women can be given either TIV or LAIV, and they do not need to avoid contact with those recently vaccinated with LAIV.[52]

COST

A potential barrier to influenza vaccination is cost. As of August 2011, the CDC listed the following prices per dose:[61]

- TIV (from various manufacturers): $10–$14
- TIV high-dose: $25
- TIV intradermal: $15.50
- LAIV: $19.70

When these prices are compared with those of antiviral drugs that can be given for influenza, the cost savings are apparent. Oseltamivir phosphate (Tamiflu, Genentech/Roche) costs approximately $9 per dose and is given as 75 mg once daily for 10 days (as prophylaxis) or 75 mg twice daily for 5 days (as treatment). If patients cannot tolerate oseltamivir, zanamivir inhalation powder (Relenza, GlaxoSmithKline) can be given. The cost is about $2 per dose, and the product is given as two inhalations once daily for 10 days (as prophylaxis) or as two inhalations twice daily for 5 days (as treatment).[62]

CONCLUSION

Vaccination is undoubtedly the best way to prevent, control, and decrease the socioeconomic burden of influenza. In order to effectively immunize all appropriate persons against influenza, various vaccines have been developed or are currently under investigation. Patients can choose to receive either the standard 45-mcg inactivated injection, the live intranasal vaccine (if appropriate), or the newly approved intradermal vaccine. Elderly patients also have an additional choice of a high-dose inactivated vaccine that contains 60 mcg per influenza strain. Whichever vaccine is used, patients should be encouraged to be immunized annually.

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